REMARKS/ARGUMENTS

The Examiner and his Primay are thanked for the courtesy of the interview at the PTO on November 9, 2004.

Claim 16 has been amended to correct a spelling error.

Claims 16 to 25 and 27 to 30 have been rejected under 35 U.S.C. §103(a) as unpatentable over CA 2,068,366 to Morella et al. ("CA '366") in view of U.S. Patent No. 5,635,200 to Douglas et al. ("Douglas"). It is submitted this rejection is improper and should be withdrawn.

The present invention is a pharmaceutical formulation. The background of this invention has been extensively discussed in the Amendment Under Rule 111 of April 23, 2004.

Applicants discovered that the presence of "fine" drug particles leads to an increased rate of drug release after coating with a polymer. This was thought to be due to the increased drug surface area that in turn led to a thinner polymer coating when common amounts of polymer were utilized. Initially, the Applicants thought (as did others in the art) that control of drug particle size was the only important factor. Applicants subsequently discovered that particle shape was potentially an important parameter. Two test batches, D4426 and D4427, were treated to determine the effect of needle shaped particles. Attached to the previously submitted Lukas Declaration are electron micrographs of powder of test batches D4426 and D4427. Batch D4426 was utilized as supplied by the supplier. As can be readily seen from the electron micrograph in Batch D4426 (which details the material provided by the supplier), a certain number of particles are effectively oblong in shape and contain sharp edges and are outside the now claimed aspect ratio. In contrast, the electron micrograph of Batch D4427 does not demonstrate particles with these dimensions. Further, a more homogenous particle size distribution also improves the performance characteristics. When these batches of particles were subjected to the process described, it was found that the needle shaped particles produced a material where 19% of the material was released after 40 minutes which is unacceptably high. In contrast, the more homogeneous batch D4427 only demonstrated 8% release after 40 minutes. This was therefore an acceptable release profile. The results of these trials are discussed in the previously submitted Lukas Declaration.

The spray drying process as described in the present application as understood by one skilled in the art involves the dispersion of the active constituents and the polymeric coating in a solvent followed by evaporation of the solvent through the use of a spray dryer. Generally, the solubility of the drug to be used in the solvent is lower than the solubility of the coating agent in the

solvent. Accordingly, as the solvent particles evaporate, the active agents crystallize and a liquid coating, which comprises the solvent and the still dissolved coating polymer, form about them. With continued solvent evaporation, the coating polymer is no longer soluble in the remaining solvent and crystallizes forming a continuous polymer coating around the active drug (which acts as a seed crystal for the polymer). This leads to the improved coating properties of the present invention as it affords almost a discrete core of active constituent surrounded by a discrete polymer coating. Furthermore, in some cases of spray drying the solvent is chosen so as not to dissolve the active ingredient at all i.e. the active ingredient stays crystalline throughout the process, and during the spray drying process the polymeric coating dries around the already crystalline active ingredient.

Claims 16 to 25 and 27-30 have been rejected based on CA 2068366 to Morella et al. ("Morella") in view of U.S. Patent No. 5,635,200 to Douglass et al. ("Douglass"). It is submitted the rejection is in error and should be withdrawn.

On page 2 of the Official Action, the Examiner states that the previously submitted argument was not convincing because "Morella et al. teaches a powder obtained by spray drying a solution of ethyl cellulose and paracetamol to obtain a powder capable of exhibiting taste masking and sustained release of paracetamol. Example 1 of Morella et al. ... at pH 6.8." However, the Examiner ignores in this analysis that Morella's Example 1 shows a formulation wherein the coating weight is at least 50% of the composition. Therefore, the Examiner's comment does not address the substance of the argument or the claimed invention.

The Examiner on page 3 of the Official Action dismisses the previously submitted argument as non-persuasive stating that Morella teaches the aspect ratio of the claimed invention and that it is within the broad scope cited by Morella. However, Morella's disclosure related only to the particle size of the active ingredient not of the pharmaceutical composition. Further, none of the embodiments disclosed or suggested in Morella show a sustained release of the order illustrated by Batch D4427.

The Examiner continues that he also relies on Douglass to teach that the spherical particles (an aspect ratio of 1) are preferred and that the motivation for preparing composition of spherical particles need not be the same as in the prior art. However, as previously pointed out, the coating weight in Douglass is substantially higher than the limit recited in the present claims. The Examiner's selection of one parameter of Douglass' disclosure while ignoring the remainder of the

parameters of the Douglass disclosure is improper. See 35 U.S.C. 103 which requires that the art be considered "as a whole."

The Examiner cites to page 4, lines 15 to 23, and contends that the reference shows that the coating of the dosage form can be from 10 to 80% of the formulation. However, such statements cannot be taken alone out of context from this multipage document. For example, at page 15, line 16 to 26, the reference lists the different parameters which are involved to obtain a microcapsule coating composition with a particular release profile for the material. In view of this extensive list of parameters, it is submitted that while the reference may use broad language to describe the wt. -% of the coating, the Examiner must consider the entire reference. The reference examples show that the coating weight of the dosage forms varies from a low of approximately 30% to a high of 55%. In this regard, the Examiner should note that methylene chloride (a.k.a. dichloromethane) is the named solvent used in the spray drying operation, is flashed off during the spray drying procedure and is not part of the dosage form product. Of particular significance is Example 6 which is a comparative example which incorporates a coating weight of approximately 27 wt.-%. The product of that comparative example is viewed under a scanning electron microscope ("SEM") and the results illustrate that the product exhibited little taste-masking consistent with the porous structure of that product as is illustrated in reference Figures 7(a) and (b).

None of the reference examples appear to illustrate a dosage form wherein the coating weight is as little as 10% or even less than the limit ("23%") now set forth in the pending claims. Thus, CA '366 does nothing more than extend an invitation to experiment and does not provide sufficient guidance to one of ordinary skill in the art to obtain a dosage form with both taste masking and sustained release properties when produced by a spray drying process with a coating weight of 23 wt.-% or less. CA '366 does no more than confirm Applicant's statement on page 1, lines 28 to page 2, line 3, of the specification that coating weights less than 24% gave unsatisfactory taste masking when that dosage form was produced by spray drying procedures. The Morella reference itself establishes in Example 6 that coating weights as low as 27 wt.-% do not give taste masking properties. CA '366 does not exemplify an embodiment with such a relatively low coating weight. Thus, the disclosure relied on by the Examiner is not actually an enabling disclosure for the purpose for which it is cited.

The Examiner states that since Example 6 is a comparative example in Morella, Example 5 is a more appropriate example. However, Example 5 has a coating weight of 28%. Figure 6 of

Morella shows the release rate for Example 5. It is instructive to compare the release rates of the compositions illustrated in Figure 6 of Morella to the release rate of Batch D4427. Batch D4427 was identified in connection with the previously submitted Lukas Declaration. Batch D4427 showed 8% release after 40 minutes. However, Figure 6 of Morella shows that after 40 minutes approximately 18% was released in the embodiment where the inlet air was dry and over 35% was released in the embodiment where the inlet air was ambient. It is noteworthy that to the extent Morella provides any release data for any of the examples or embodiments specified in the reference, none show the degree of sustained release indicated by the attachments to the Lukas Declaration. Figure 4 of Morella, which shows release rates for numerous active ingredient coated with an ethyl cellulose membrane, indicates that the lowest rate of release was for paracetamol and after 40 minutes, this release rate was approximately 15 to 16%, approximately double that exhibited by Batch D4427. The improvement in sustained reference exhibited by the now claimed invention is thus unexpected.

At the interview on November 9, 2004, it was agreed that the Examiner would consider what he might find acceptable as a showing to overcome the obviousness rejection. Applicant's counsel contacted both the Examiner and his Primary Examiner but never received any suggestions for a suitable showing.

While applicant disagrees that the Examiner has made out a prima facie case, it is submitted that the Lukas declaration overcomes the obviousness rejection.

On page 6 of the Office Action, the Examiner again refers to Morella's Example 5 and acknowledges that the composition of Example 5 had a 28% coating weight. The Office Action is unclear as to how this addresses that in the prior art coating weights of less than 24% gave unsatisfactory taste masking when that dosage form was produced by spray drying procedures.

Douglas relates to taste masking compositions of ranitidine and specifically to ranitidine hydrochloride. Douglas' comment as to particle size is based on his desire to avoid a "gritty" feel in the mouth.

In Douglas, the active ingredient is first coated with a lipid phase. The lipid coating is selected from fatty acids (or monohydric alcohols of those fatty acids), fixed oils, fats, sterols, phospholipds, glycolipids and mixtures thereof. The lipid coated particles of ranitidine are then encased in a binder selected from the group of polyvinyl pyrrolidone, acrylate polymers and cellulose based polymers. The coating weights in Douglas far exceed the upper limits specified in

the now pending claims. In fact, it appears that the coating weight percentages of the Douglas examples exceed even the highest coating wt. -% of those exemplified in CA '366. Each of examples 1 to 3 of Douglas shows the ranitidine hydrochloride content of the final dosage form as 20 wt. -% suggesting that the combined coating and binder weights were approximately 80% in each instance. The particles produced by Example 4 have four times the weight of the tripalmitate relative to the ranitidine hydrochloride. The particles produced in Example 5 also have four times the tristerate and trilaurate relative to the active ingredient. Examples A through G of the reference use artificial sweeteners such as xylitol, peppermint flavoring, aspartame and combinations thereof. It appears that in each of Examples A through G, the active ingredient comprises no more than 20 wt. -% of the dosage form suggesting that the coating and sweetener weights constitute 80 wt.-%.

While the Examiner may be relying on Douglas only for the discussion of the aspect ratio or physical shape of the particles used by Douglas, it is submitted that the command of 35 U.S.C. §103 requires that the entirety of the reference be considered. In this regard, it should be noted that Douglas provides absolutely no information as to the dissolution characteristics of his dosage forms. That is to say, one cannot tell whether those dosage forms are sustained release, controlled release or immediate release products. Douglas' disclosure as to the weight ranges for the lipid and for the binder make it clear that a product according to Douglas could not have a coating weight of 23 wt.-% or less. The Examiner has virtually ignored this argument and on pages 6 and 7 of the Official Action of October 4, 2004 and merely repeated his limited reliance on Douglass.

Claim 26 has been rejected under 35 U.S.C. §103(a) based on the combination of CA '366 in view of Douglas and further in view of U.S. Patent No. 4,808,411 to Lu et al. ("Lu") or U.S. Patent No. 5,707,646 to Yajima et al. ("Yajima"). It is submitted that this rejection is also improper and should be withdrawn.

Nothing in the Office Action discussion of the Yajima or Lu '411 references or in either of the references indicates that a substantially continuous polymer coating is formed and that the resulting product has sustained release properties or that the coating comprises less than 23% by weight of the formulation.

The Lu '411 reference discloses a complex of carbomer (acrylic acid polymers) and erythromycin or a derivative thereof. Lu's compositions are prepared by dispersing the drug, such as erythromycin, in a suitable organic solvent such as ethanol or acetone, and dispersing the carbomer separately in ethanol, mixing the two solutions slowly to allow formation of the reaction

product and then evaporating most of the solvent and diluting the solution with water. The reaction product is recovered by filtration and is then dried. No mention is made of spray drying or spray dried particles. This reference gives no indication of the weight percent of the coating. The Examiner apparently cites Lu for its disclosure of particle size range. However, none of the particle size ranges disclosed in Lu correspond with, or suggest, those set forth in the pending claims. A mention in a reference of particles smaller than 297 microns does not disclose or suggest the parameters set forth in the now pending claims.

Yajima relates to a taste masked pharmaceutical formulation comprising clarithromycin but is no more pertinent than Lu '411 as discussed above.

In summary, Applicants have discovered the parameters in relation to the use of a small amount of polymer coating to successfully achieve taste masking and sustained release properties for pharmaceutically active compounds. These parameters include control of the shape of the core particle which leads to a product with successful performance characteristics.

As shown above, based on the prior art, the release and/or taste masking properties obtained were inconsistent which is not acceptable for pharmaceutical administration. In contrast, formulations in accordance with the present invention exhibit consistency of taste masking and sustained release, leading to improved results. See the previously submitted Lukas Declaration. Accordingly, it is respectfully submitted that the invention is not obvious in view of the art.

The Examiner in the Office Action has failed to address applicant's previously submitted arguments regarding the Liu or Yajima reference. It once again appears that since the Examiner has relied on only selected disclosure from each of the references, he considers the remainder of the reference content as not relevant and accordingly is in violation of the command of 35 U.S.C. 103 that the art be considered as a whole.

On page 8 of the Official Action there is a heading "Response to Declaration". However, the discussion included under that heading fails to address the declaration substance. Rather, it is merely a repeat of the Examiner's comments regarding the previously cited art.

It is submitted that the Official Action should not contain a final rejection. The Office Action fails to address the previously submitted arguments and substance and therefore is improper in that it does not assist in defining the issues. Thus, the final rejection is premature. The Examiner has failed to address the substance of the previously submitted Lukas Declaration. This is improper see *In re Piasecki*, 223 U.S.P.Q. 785 (Fed. Cir. 1984). Further, as indicated in the MPEP §706.07,

before a final rejection is in order, a clear issue should be developed between the Examiner and the applicant. The Examiner, having ignored the substance of the Lukas Declaration, certainly has not developed a clear issue.

It is further submitted that the combinations of references are improper. As discussed above, each of the references list different techniques to obtain different products with different characteristics. It is clear that the Examiner has engaged in a pick and choose technique based on hindsight using Applicants' invention as a blueprint to selectively edit the cited references. This is improper. See *In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985). Further, the manner in which the Examiner has edited the references for the combination would require that salient features of the respective disclosures of the references and important features of the inventions as disclosed therein be ignored. Note the different coating weight in CA '366 and Douglas as well as the different coating techniques. This is also improper for a rejection under 35 U.S.C. §103. See *In re Ratti*, 123 U.S.P.Q. 349 (CCPA 1959).

In view of the foregoing, reconsideration and allowance of the application with claims 16 to 30 are earnestly solicited.

It is believed that no additional fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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Dated: January 4, 2005